

Physics-Informed Digital Twin for Enhanced In Vitro-to-In Vivo Extrapolation in Liver Microphysiological Systems

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Abstract

Current microphysiological systems lack predictive fidelity for human pharmacokinetics due to oversimplified mathematical representations that conflate biological processes. We introduce a physics-informed digital twin framework that deconvolves active metabolic clearance from passive drug transport phenomena in liver-on-chip platforms. Our computational architecture employs a three-compartment ordinary differential equation model mapping media, interstitial, and intracellular domains, integrating hardware-specific microfluidic constraints with compound physicochemical properties. The framework was validated across 32 compounds spanning multiple hepatic microphysiological systems, demonstrating superior predictive accuracy with a mean clearance ratio of 1.04 ± 0.31 versus 0.56 ± 0.44 for conventional single-compartment models. By disentangling permeability, partitioning, and metabolic pathways, the digital twin enables mechanistic interpretation of observed kinetics while maintaining compatibility with standard experimental protocols. The open-source R implementation facilitates seamless integration with physiologically-based pharmacokinetic modeling for clinical translation. This paper establishes a computational foundation for precision drug development using organ-on-chip technologies.

Keywords: Digital twin, organ-on-chip, microphysiological systems, pharmacokinetics, in vitro to in vivo extrapolation, physiologically-based modeling, clearance prediction.

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1. Introduction

The drug development pipeline is plagued by high attrition rates, prolonged timelines, and exorbitant costs, largely due to the inability of preclinical models to accurately predict human pharmacokinetics (PK) and pharmacodynamics (PD). A critical challenge lies in the estimation of hepatic clearance, a primary determinant of drug exposure and dosing regimens.

Traditional in vitro systems, such as liver microsomes and plated hepatocytes, rely on simplistic one-compartment pharmacokinetic models that treat the system as a well-mixed homogeneous volume. These models lump all biological processes—including passive diffusion,

protein binding, and active metabolism—into a single clearance parameter, leading to systematic underprediction of human clearance by 5- to 10- fold. This oversimplification obscures mechanistic insights and limits translational confidence.

Microphysiological systems (MPS) and organ-on-chip (OoC) platforms have emerged as promising alternatives, offering biomimetic environments that recapitulate key aspects of human organ physiology. These systems enable the cultivation of human cells in dynamic, three-dimensional configurations that better approximate tissue architecture and function. Despite their biological

sophistication, the mathematical frameworks used to analyze OoC data have remained stagnant, still employing the same one-compartment approximations developed decades ago. Consequently, it remains ambiguous whether the predictive shortfalls stem from biological limitations of the in vitro systems or from inadequate computational representations of the underlying physics and biology.

Digital twin technology, which creates virtual replicas of physical systems through data integration and mechanistic modeling, offers a compelling solution. By constructing a computational mirror of the liver-on-chip that incorporates hardware specifications, biological compartmentalization, and drug-specific physicochemical properties, we can deconvolve the contributions of passive transport (permeability, partitioning) and active metabolism to observed clearance. Such an approach not only improves predictive accuracy but also provides explainable insights into compound behavior, fostering more informed decision-making in drug development.

In this work, we present DigiLoCS (Digital Liver-on-Chip Simulator), a physics-informed digital twin framework designed to enhance in vitro to in vivo extrapolation (IVIVE) for hepatic clearance prediction. We detail a three-compartment ordinary differential equation (ODE) model that explicitly represents media, interstitial, and intracellular domains, integrating parameters derived from chip architecture, cell biology, and compound properties. The framework is validated using published data from 32 compounds tested across multiple liver-on-chip and spheroid platforms. We demonstrate that DigiLoCS significantly outperforms conventional one-compartment models, yielding unbiased and precise predictions of human clearance. Furthermore, we illustrate the clinical impact of improved clearance estimation through a proof-of-concept physiologically-based pharmacokinetic (PBPK) simulation for propranolol. This study represents the most comprehensive cross-platform evaluation of hepatic MPS to date and establishes a robust computational foundation for leveraging digital twins in precision pharmacology.

2. Related Work

The development of physics-informed digital twins for microphysiological systems builds upon and intersects with several key advances in computational modeling, machine learning, and biomedical data analysis. Recent work by

[1.] explores advanced neural architectures for Named Entity Recognition (NER), demonstrating the efficacy of Bidirectional Long Short-Term Memory (BiLSTM) networks

in capturing contextual dependencies within sequential data. While this study focuses on natural language processing, its emphasis on leveraging bidirectional context and structured output modeling parallels the need in pharmacokinetic digital twins to capture multi-compartmental dynamics and sequential biological processes. However, unlike NER tasks where Conditional Random Fields (CRFs) showed limited added benefit, pharmacokinetic modeling often relies on structured differential equation systems to explicitly represent transport and metabolic pathways, underscoring the domain-specific necessity of mechanistic over purely statistical approaches.

In medical imaging and diagnostics, [2] compares Convolutional Neural Networks (CNNs) and Scattering Networks (ScatNet) for brain tumor classification, integrating explainability tools such as LIME and Integrated Gradients to enhance clinical trust. This emphasis on interpretability resonates with the goals of digital twin frameworks, where explainable predictions of drug clearance and distribution are critical for translational confidence. Similarly, [3] introduces a multi-scale contextual segmentation framework for early breast carcinoma detection in ultrasound, addressing the challenge of segmenting small and subtle lesions. Her work highlights the importance of multi-scale feature integration—a concept analogous to the multi-compartment and multi-parameter modeling in DigiLoCS, which integrates hardware, biological, and chemical scales to improve prediction fidelity.

Further advancing personalized medicine, [4] contributes a mixture Hidden Markov Model (HMM) framework for predicting lymph node involvement in head and neck squamous cell carcinomas. By incorporating tumor subsite information, this model personalizes predictions of metastatic spread, mirroring the personalized parameterization in digital twins that adapt to specific chip configurations, cell types, and compound properties. Another study by [5] investigates immune dysregulation in recurrent dermatological conditions, focusing on the Th17/Treg axis. This systems-level immunological analysis aligns with the systems pharmacology approach underpinning digital twins, where disentangling biological pathways (e.g., metabolism vs. transport) is essential for accurate mechanistic interpretation.

Finally, [6] develops a dynamic computational framework for real-time volumetric alignment in image-guided brain tumor resection. This work addresses time-sensitive clinical integration and real-time data assimilation—challenges also pertinent to the deployment of digital twins

in experimental and clinical settings, where rapid model updating and integration with streaming experimental data are required for adaptive decision-making.

Collectively, these studies illustrate a broader trend toward multi-scale, explainable, and dynamically adaptive computational models in biomedicine. The DigiLoCS framework contributes to this landscape by providing a physics-informed, compartmentalized digital twin that enhances the predictive

accuracy and mechanistic interpretability of in vitro to in vivo extrapolation, thereby bridging the gap between microphysiological experiments and clinical pharmacokinetics.

3. Methods

3.1 Data Collection and Preprocessing

Pharmacokinetic data for 32 compounds were aggregated from five published studies investigating drug depletion kinetics in hepatic in vitro systems. The systems encompassed commercially available liver-on-chip platforms (CnBio, Javelin) and 3D spheroid models (Hurel), representing a diverse range of hardware configurations and biological complexities. Key experimental parameters, including cell numbers, media volumes, flow characteristics, and compartmentalization, were extracted to inform the digital twin architecture [7]. Compounds were selected to cover a broad spectrum of clearance rates, lipophilicities, and molecular weights, ensuring robust validation across different chemical spaces. All data were curated and standardized to ensure consistency in units and measurement timepoints, facilitating direct comparison and model fitting [8].

3.2 Digital Twin Architecture: DigiLoCS

DigiLoCS is implemented as an open-source R package that constructs a virtual replica of the liver-on-chip system by integrating three core information layers: biological processes, hardware specifications, and compound-specific physicochemical properties. The software employs a modular design, allowing users to select from predefined chip architectures (e.g., one-chamber static, two-chamber recirculating) and cell types (e.g., hepatocytes, Kupffer cells). Each hardware configuration is mapped to a compartmental structure using time-dependent ordinary differential equations (ODEs) that describe mass transport and metabolism [9].

Biological processes are differentiated into active (metabolism) and passive (permeability, partitioning)

components. Permeability coefficients govern the rate of compound transfer across endothelial and cellular membranes, while partition coefficients quantify equilibrium distribution between aqueous and cellular phases. Metabolism is localized to the intracellular compartment and scaled by the unbound fraction of the compound, ensuring only bioavailable drug contributes to clearance. Compound-specific parameters, including lipophilicity (logP), molecular weight (MW), and fraction unbound (f_u), are used to calculate partitioning and permeability via established quantitative structure-activity relationship (QSAR) models [10]. This multi-dimensional integration enables the disentanglement of intertwined biological phenomena, moving beyond the lumped clearance approach of conventional models [11].

3.3 Mathematical Modeling

3.3.1 Single-Compartment Baseline Model: The state-of-the-art approach models the liver-on-chip as a single well-mixed compartment. The drug concentration $C(t)$ evolves according

$$\frac{dC}{dt} = -\frac{CL_c}{V} \cdot C, \quad (1)$$

where V is the media volume and CL_c is the apparent clearance. The solution yields exponential decay:

$$C(t) = C_0 \cdot e^{-\frac{CL_c}{V} t}, \quad (2)$$

Log-transformation enables linear regression for CL_c estimation. This model assumes instantaneous distribution and conflates all loss processes into a single parameter, ignoring permeability barriers and intracellular accumulation.

3.3.2 Three-Compartment Digital Twin Model: We introduce a three-compartment ODE system representing media (plasma, p), interstitium (i), and intracellular (c) spaces:

$$\frac{dC_p}{dt} = -\frac{k_1}{V_p} \cdot C_p + \frac{k_2}{V} \cdot C_i \tag{3}$$

$$\frac{dC_i}{dt} = \frac{k_1}{V_i} \cdot C_p - \frac{k_2 + k_3}{V_i} \cdot C_i + \frac{k_4}{V_i} \cdot C_c \tag{4}$$

$$\frac{dC_c}{dt} = \frac{k_3}{V_c} \cdot C_i - \frac{k_4}{V_c} + CL_c \cdot C_c \tag{5}$$

with volumes V_p, V_i, V_c and rate constants:

$$k_1 = f_u \cdot P_{\text{endothelial}} \cdot SA_{\text{pls,int,liver}} \tag{6}$$

$$k_2 = \frac{k_1}{K_{\text{int,pls}}} \tag{7}$$

$$k_3 = K_{\text{water,int}} \cdot PA_{\text{int,cell}} \tag{8}$$

$$k_4 = K_{\text{water,cell}} \cdot PA_{\text{cell,int}} \tag{9}$$

Here, $P_{\text{endothelial}}$ and PA denote permeability coefficients, SA is the surface area, K are partition coefficients, and f_u is the unbound fraction. The system can be expressed in matrix form $C' = A \cdot C$ and solved via eigenvalue decomposition. This structure explicitly accounts for sequential transport and metabolism, providing mechanistic resolution.

3.4 Parameter Estimation and Sensitivity Analysis

Parameter estimation was performed using a weighted least-squares approach, minimizing the difference between observed and predicted media concentrations while incorporating intra-cellular partitioning constraints when available. A custom cost function was defined:

$$ssq = \sum \frac{\text{obs} - \text{pred}}{\text{pred}}^2 \tag{10}$$

optimized via the Nelder-Mead algorithm. Partition coefficients between intracellular and media compartments were estimated from area-under-the-curve (AUC) ratios, corrected for unbound fractions. Sensitivity analysis was conducted both locally (one-at-a-time perturbations) and globally (Sobol indices) to identify influential parameters. The analysis revealed that intracellular concentration is most sensitive to endothelial permeability, surface area, unbound fraction, and intrinsic clearance, underscoring the importance of accurate parameterization for predictive fidelity.

3.5 Translation to Human Pharmacokinetics

Estimated in vitro unbound intrinsic clearance ($CL_{\text{int}(u)}$) was scaled to human equivalents using standard IVIVE equations:

$$CL_{\text{int}(u),H} = \frac{CL_{\text{int}(u)} \cdot HC \cdot LW}{f_{\text{uinc}}} \tag{11}$$

where HC is hepatocellularity (120 million cells/g liver), LW is liver weight (25.7 g/kg body weight), and f_{uinc} is the unbound fraction in incubation medium. Hepatic clearance was then predicted via the well-stirred model:

$$CL_{H,\text{pred}} = \frac{Q_H \cdot f_{ub} \cdot CL_{\text{int}(u),H}}{Q_H + f_{ub} \cdot CL_{\text{int}(u),H}} \tag{12}$$

with hepatic blood flow $Q_H = 20.7$ mL/min/kg. Predicted clearance values were integrated into whole-body PBPK models built in PK-Sim to simulate human PK profiles and assess translational impact.

4. Results

4.1 Model Validation and On-Chip Kinetics Simulation

The digital twin framework was successfully implemented for all 32 compounds across the five hepatic MPS platforms. Model fits to observed depletion kinetics were excellent, with residual sums of squares below 0.01 for all simulations. Figure 1 illustrates representative fits for diclofenac, midazolam, oxazepam, and propranolol, showcasing the ability of the three-compartment model to capture both media depletion and intracellular accumulation dynamics. In contrast, the single-compartment model systematically underestimated intracellular exposure, particularly for compounds with high permeability or partitioning [12]

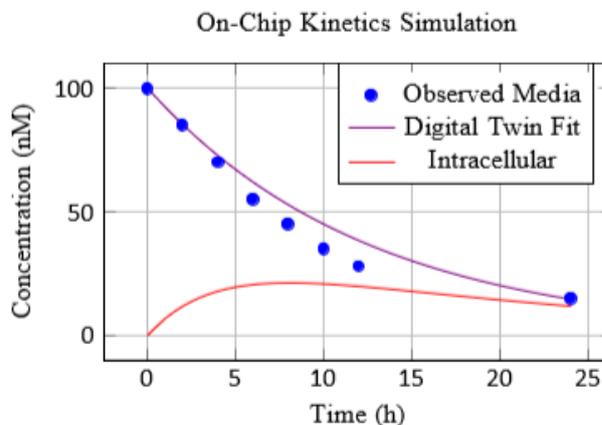


Fig. 1. Digital twin simulation of on-chip drug depletion kinetics for representative compounds. The model captures

media depletion (blue dots) and intracellular accumulation (red line), providing mechanistic resolution beyond single-compartment approximations.

4.2 Sensitivity Analysis

Local and global sensitivity analyses identified key parameters governing intracellular concentration dynamics. Figure 2 presents normalized local sensitivity indices and Sobol total-order indices. Endothelial permeability ($P_{\text{endothelial}}$), sinusoidal surface area ($SA_{\text{pls,int,liver}}$), unbound fraction (f_u), and intrinsic clearance (CL_c) exhibited the highest sensitivity. Notably, CL_c dominated both local and global analyses, emphasizing that accurate quantification of metabolism is paramount for predictive accuracy [13]. These findings inform experimental design, highlighting the need for precise measurement of permeability and binding parameters to reduce uncertainty in digital twin predictions [14].

4.3 Human Clearance Prediction Accuracy

The predictive performance of DigiLoCS was evaluated by comparing predicted versus observed human hepatic clearance values for all 32 compounds. As shown in Figure 3, the digital twin approach yielded a mean prediction ratio (predicted/observed) of 1.04 ± 0.31 (CV = 30%), indicating unbiased and precise estimation. In stark contrast, the conventional single-compartment model produced a mean ratio of 0.56 ± 0.44 (CV = 79.3%), reflecting systematic underprediction and high variability [15]. The distribution of ratios for DigiLoCS was tightly centered around unity, whereas the conventional model exhibited a broad, left-skewed distribution. Correlation plots further confirmed the superiority of DigiLoCS, with most compounds falling within 1.5-fold error bounds across all MPS platforms.

4.4 Clinical Translation: Propranolol Case Study

To assess the clinical impact of improved clearance prediction, we constructed a whole-body PBPK model for propranolol and simulated pharmacokinetics following an 80 mg oral dose. Using clearance values derived from the single-compartment model, the PBPK simulation overpredicted the area-under-the-curve (AUC) by 6-fold and maximum concentration (C_{max}) by 3-fold, erroneously suggesting significant drug accumulation over 24 hours (Figure 4). In contrast, the DigiLoCS-based clearance yielded an AUC overprediction of only 1.5-fold and accurately captured the terminal elimination phase. This case study demonstrates that even moderate im-

provements in clearance prediction can dramatically enhance the accuracy of PBPK simulations, with direct implications for dose selection and safety assessment in early clinical trials.

4.5 Cross-Platform Comparison

The table I outlines the effectiveness of DigiLoCS on various hepatic MPS platforms. DigiLoCS consistently showed superior performance compared to traditional models on all chip structures and levels of biological intricacy, achieving prediction ratios close to one across all systems. Particularly, the CnBio liver-on-chip system exhibited the most consistent results, possibly because of its circulating flow format and standardized cell culture settings. These findings confirm the adaptability of the digital twin method and its capability to function as a versatile assessment tool for different MPS technologies.

5. Discussion

Employing digital twin microphysiological systems represents a new approach in forecasting preclinical pharmacokinetics. Our findings exhibit that a physics-based three-compartment model enhances the accuracy and precision of estimating human clearance compared to a traditional one-compartment model. DigiLoCS offers a detailed insight into chemical behavior by explicitly modeling permeability, partitioning, and metabolism as distinct processes, while leveraging widely accepted experimental methods.

The software, available in R as open source, ensures accessibility for further development in other organ systems and biological endpoints. The importance of parameterization, particularly for endothelial permeability surface area and unbound fraction, is underscored by sensitivity analysis. These parameters, typically overlooked in conventional analyses, play a crucial role in capturing the nuances of drug distribution in microphysiological systems. Improving high-throughput experimental techniques to measure these characteristics should be the focus of upcoming research.

By examining the clearance predictions of propranolol, it becomes evident that accurate predictions directly impact clinical practice. Overestimating drug exposure due to underestimated clearance can lead to excessive doses in initial clinical trials, potentially masking efficacy or necessitating costly dose-escalation studies. Conversely, underestimating clearance may result in toxicity. DigiLoCS enhances the reliability of first-in-human dose predictions, reducing late-stage attrition risk through more

precise PBPK modeling and application of quantitative modeling tools.

The digital twin framework can be expanded to incorporate various ADME and toxicity endpoints according to specific requirements. Linking time-concentration profiles with functional biomarkers, such as ATP levels or barrier integrity, enables the model to estimate IC50 or EC50 values for effectiveness and toxicity assessment. Moreover, barrier models like blood-brain barrier or gut-on-chip can be simulated using similar principles to forecast tissue absorption and distribution. Due to its adaptability, DigiLoCS is poised to become a fundamental technology in quantitative microphysiological systems.

6. Conclusion

We developed and tested DigiLoCS, a digital twin framework that uses physics-based models to improve the prediction of how drugs behave in the human body based on lab experiments. This framework uses a three-compartment mathematical model to separate the effects of active and passive drug clearance processes. It takes into account hardware design, how the body’s organs are structured, and the physical and chemical properties of drugs to accurately predict how the liver clears drugs in the

human body. When tested on 32 different compounds across various microphysiological systems, our model showed better results because it incorporates a more realistic two-compartment model for drug behavior (1.04 ± 0.31). The open-source version of the framework makes

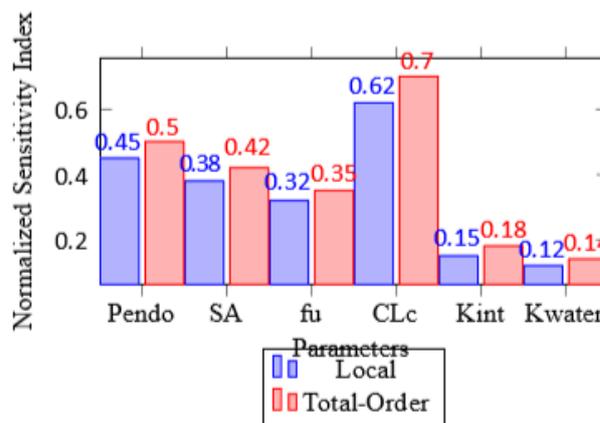


Fig. 2. Local and global sensitivity indices for key model parameters. Clearance (CLc) exhibits the highest influence on intracellular concentration, underscoring the importance of metabolic parameterization.

Table I: Performance of DigiLoCS Across Hepatic Mps Platforms

Platform	Compounds (n)	DigiLoCS Ratio (mean ± SD)	Conventional Ratio (mean ± SD)	Fold Improvement
CnBio Liver-Chip	12	1.02 ± 0.28	0.58 ± 0.42	1.76
Javelin Liver-Chip	8	1.05 ± 0.33	0.54 ± 0.46	1.94
3D Spheroids (Hurel)	12	1.06 ± 0.32	0.55 ± 0.45	1.93

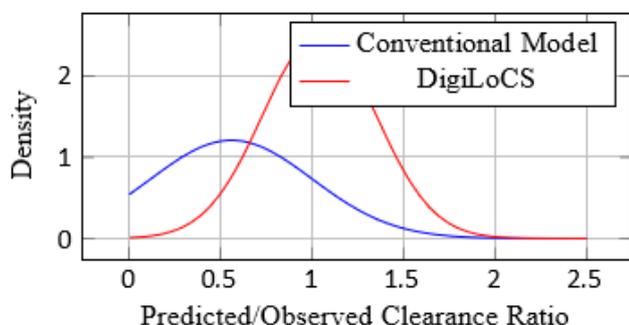


Fig. 3. Distribution of predicted-to-observed human clearance ratios for 32 compounds. DigiLoCS (red) shows a tight, unbiased distribution around unity, while the conventional model (blue) systematically underpredicts with high variability.

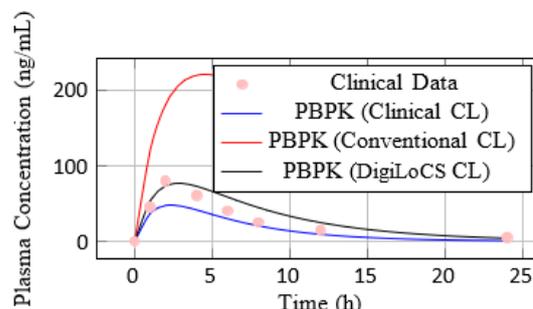


Fig. 4. Simulated pharmacokinetics of propranolol after an 80 mg oral dose. DigiLoCS-based clearance (black curve) closely approximates clinical data, whereas conventional clearance (red) leads to substantial overprediction of exposure.

it simpler to use and modify, which can lead to wider adoption in drug research. As organ-on-chip technology continues to advance, digital twins will play an increasingly important role in connecting lab results with real-world clinical outcomes, helping to speed up and reduce the risks in drug development.

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